effective amount of a composition comprising palivizumab or one or more fragments thereof that immunospecifically bind to one or more RSV antigens, wherein said therapeutically effective amount results in a therapeutically effective concentration of at least 20 ng per mg of lung protein at least 20 days after the administration of said first dose and prior to the administration of a subsequent dose.

189. (once amended) The method of claim 180 or 181, wherein the human subject is a human subject which has had a bone marrow transplant, an elderly human subject, or a human subject which has cystic fibrosis, bronchopulmonary dysplasia, congenital heart disease, congenital immunodeficiency or acquired immunodeficiency.

190. (once amended) The method of claim 180 or 181, wherein the human subject is a human infant.

191. (once amended) The method of claim 180 or 181, wherein the human subject is a human infant born prematurely or is at risk of hospitalization for a RSV infection.

REMARKS

At the outset, Applicants and Applicants' representatives thank Examiner Stacy Brown for the courtesy of the interview conducted on April 30, 2003 in connection with the above-identified application. The amendments and the remarks made herein reflect the discussion that took place during the interview.

Claims 73, 74, 85-110, 180, 181, 186, 187, 189-191, and 200-230 were pending in this application. Applicants have canceled claims 95-98 and 200-230, without prejudice to Applicants' rights to pursue the subject matter of the canceled claims in related applications. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejections, Applicants have also amended claims 85-88, 99-110 180, 181 and 189-191 to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention. In particular, claim 86 has been amended to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering to a human subject an amount of a palivizumab sustained release formulation that results in an effective neutralizing titer of palivizumab. Claim 88 has been amended to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering to the lungs of a human subject an amount of a palivizumab pharmaceutical composition adapted for pulmonary delivery that results in an effective

neutralizing titer of palivizumab. Claims 85 and 87 have been amended to recite a human subject. Claims 99-110 have been amended to change their dependencies in view of the cancellation of claims 94-98. Claims 180, 181 and 189-190 have been amended to recite a method of preventing a RSV infection, or treating or ameliorating one or more symptoms associated with a RSV infection in a human subject.

A marked up version of the claims amended herein, with deletions indicated by brackets and additions indicated by underlining, is attached hereto as Exhibit A. The amended claims are fully supported by the specification of the instant application, see, *e.g.*, page 20, lines 19-22, page 23, lines 3-6, page 24, lines 1-5, page 24, lines 23-29, page 25, lines 2-10, page 27, lines 17-21, and page 83, lines 21-34, and do not constitute new matter. Upon entry of this amendment, claims 73, 74, 85-94, 99-110, 180, 181, 186, 187 and 189-191 will be pending in the present application. For the Examiner's convenience, a copy of claims that will be pending claims upon entry of this amendment is attached hereto as Exhibit B.

The amendments and remarks made herein narrow the issues on appeal and are designed to place the case in condition for allowance. As such, Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

1. THE REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITHDRAWN

Claims 200-230 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner contends that the specification fails to provide sufficient guidance to enable one of skill in the art to obtain the titer levels recited in the claims by administering the specified dosages of palivizumab. In order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejection, Applicants' have canceled claims 200-230, without prejudice. The cancellation of claims 200-230 has obviated the rejection under 35 U.S.C. § 112, first paragraph. Accordingly, the rejection of claims 200-230 under 35 U.S.C. § 112, first paragraph, is moot and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITHDRAWN

Claims 85-110 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Examiner contends that the meaning of the phrase

"therapeutically effective amount" is unclear. Specifically, the Examiner has alleged that the meaning of "therapeutically effective" is defined according to page 30, lines 12-15 with regard to cotton rats and the definition of "therapeutically effective" for other mammals is not clear. In addition, the Examiner has also alleged that page 30 of the specification merely discloses that the phrase "therapeutically effective serum titer" indicates the amounts that reduce the severity, duration and/or symptoms associated with RSV infection and it is unclear what endpoints indicate the reduction of severity, reduction of duration and reduction of symptoms associated with RSV. For the reasons detailed below, the rejection under 35 U.S.C. § 112, second paragraph, cannot stand and should be withdrawn.

Preliminarily, Applicants note that claims 85, 87, 89, 90, 93, 95, 98, 99, 101, 103, 104, 107, 108, 109 and 110 do not recite the phrase "therapeutically effective amount." Rather, these claims recite the phrase "prophylactically effective amount." The previous Office Action mailed March 26, 2002 (Paper No. 13) stated that claims 85-110 were rejected as indefinite for the recitation of the phrases "therapeutically effective amount" and "prophylactically effective amount." However, the current Office Action only rejects claims 85-110 as indefinite for the recitation of the phrase "therapeutically effective amount." In the telephone interview conducted on April 30, 2003, Examiner Stacy Brown clarified that the rejection under 35 U.S.C. § 112, second paragraph, was only meant to apply to those claims that recite the phrase "therapeutically effective amount," *i.e.*, claims 86, 88, 91, 92, 94, 100, 102, 105, 106, 109 and 110. Accordingly, Applicants response to the rejection under 35 U.S.C. § 112, second paragraph, is directed to claims 86, 88, 91, 92, 94, 100, 102, 105, 106, 109 and 110 which recite the phrase "therapeutically effective amount."

Applicants respectfully assert that one of skill in the art would appreciate the meaning of the phrase "therapeutically effective amount" in view of the teaching in the specification of the application regarding the phrase "therapeutically effective" and assays for determining therapeutic effectiveness (see, *e.g.*, page 29, line 26 to page 30, line 15 and page 94, line 30 to page 100, line 8), and therefore, claims 86, 88, 91, 92, 94, 100, 102, 105, 106, 109 and 110 are definite. The courts have consistently held the phrase "an effective amount" to be definite where those skilled in the art would be able to determine from the written description what an effective amount is by understanding the function which is to be achieved or the use which is to be affected. See, *e.g.*, *In re Halleck*, 422 F.2d 911, 164 U.S.P.Q. 647 (CCPA 1970) and *In re Watson*, 517 F.2d 465, 186 U.S.P.Q. 11 (CCPA 1975). Accordingly, Applicants respectfully submit that one of skill would appreciate the endpoints that indicate that

effectiveness has been achieved based upon the teaching in the specification of the application.

However, in order to expedite the prosecution of the present application and without conceding to the validity of the Examiner's rejection, Applicants have canceled claims 94-98 and amended claims 86 and 88 (and claims dependent therefrom). In particular, Applicants have amended claim 86 to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering to a human subject an amount of a palivizumab sustained release formulation that results in an ***effective neutralizing titer*** of palivizumab. Applicants have amended claim 88 to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering to the lungs of a human subject an amount of a palivizumab pharmaceutical composition adapted for pulmonary delivery that results in an ***effective neutralizing titer*** of palivizumab. Thus, presently pending claims 86, 88, 91, 92, 94, 100, 102, 105, 106, 109 and 110 specify that a "therapeutically effective amount" results in an "effective neutralizing titer." The phrase "effective neutralizing titer" is defined at page 27, lines 17-21 of the specification of the application as the amount of serum present in a human that is either clinically efficacious or reduces virus by 99%, and the specification at, *e.g.*, page 94, line 30 to page 100, line 8 describes assays for determining an effective neutralizing titer. Thus, Applicants respectfully submit that one skill in the art would understand the scope of the phrase "effective neutralizing titer." Accordingly, Applicants respectfully assert that the Examiner's rejection has been obviated, and therefore, the rejection under 35 U.S.C. § 112, second paragraph, should be withdrawn.

3. THE REJECTIONS UNDER 35 U.S.C. § 102(b) SHOULD BE WITHDRAWN

Claim 74 is rejected under 35 U.S.C. § 102(b) as being anticipated by Johnson etal., 1997, *J. Infect. Dis.* 176:1215-1224 (hereinafter "Johnson"). The Examiner alleges that Johnson teaches a humanized monoclonal antibody (MEDI-493), palivizumab, and the intranasal administration of MEDI-493 to cotton rats. For the reasons detailed below, the rejection under 35 U.S.C. § 102(b) cannot stand and should be withdrawn.

It is axiomatic that for a prior art reference to anticipate a claimed invention under 35 U.S.C. § 102(b), it has to meet every element of the claimed invention. *Hybritech Inc. v. Monoclonal Antibodies, Inc.* 802 F.2d 1367, 231 U.S.P.Q. 81, 91 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987).

Contrary to the Examiner's allegation, Johnson does ***not*** teach the ***intranasal*** administration of MEDI-493. Rather, Johnson only describes the intramuscular and intravenous administration of MEDI-493 to cotton rats. Claim 74 recites a pharmaceutical composition adapted for ***pulmonary delivery*** comprising palivizumab or an antigen-binding fragment thereof. Thus, Johnson does not disclose each and every element recited in pending claim 74, and therefore, does not anticipate claim 74. Accordingly, Applicants respectfully assert that the rejection under 35 U.S.C. § 102(b) cannot stand and should be withdrawn.

4. THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 73 and 85-94 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of Lam et al., 1997, *Proc. Int'l Symp. Rel. Bioact. Mater.* 24:759-760 (hereinafter "Lam"). Claims 95-110, 180, 181, 186, 187, and 189-191 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over Johnson in view of MedImmune, Inc. Synagis® (Palivizumab) package insert (hereinafter the "Package Insert") and Lam for the reasons of record. As set forth in Paper No. 13, the Examiner contends that: (1) Johnson describes a humanized monoclonal antibody (MEDI-493; palivizumab) that prevents RSV infection; (2) the Package Insert describes the administration of Synagis® (palivizumab) to pediatric patients less than two years old; and (3) Lam describes sustained release microencapsulation pharmaceutical formulations of recombinant humanized monoclonal antibodies for patients. The Examiner alleges that it would have been *prima facie* obvious to administer the antibodies described in Johnson in the manner described in the Package Insert since they are the same antibodies. The Examiner also alleges that it would have been *prima facie* obvious to administer the antibodies described in Johnson in a sustained release vehicle as taught in Lam. For the reasons detailed below, the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

A finding of obviousness requires a determination of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed subject matter and the prior art, and whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1996). The proper inquiry is whether the art suggests the invention, and whether the art provides one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 7 U.S.P.Q. 2d 1673 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded

in the prior art and not in the Appellants' disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991).

Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination," and "teachings of references can be combined only if there is some suggestion or incentive to do so." *In re Fine* 837 F.2d 1071, 1075 (Fed. Cir. 1988).

In order to expedite the prosecution of the application and without conceding to the validity of the rejection, Applicants have amended claims 85-88, 99-110 180, 181 and 189-191 and canceled claims 95-98, without prejudice. In particular, Applicants have amended claim 86 (claims dependent therefrom) to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering to a human subject an amount of a palivizumab ***sustained release formulation*** that results in an effective neutralizing titer of palivizumab. Applicants have amended claim 88 (and claims dependent therefrom) to recite a method of treating or ameliorating one or more symptoms associated with a RSV infection by administering ***to the lungs*** of a human subject an amount of a palivizumab pharmaceutical composition that results in an effective neutralizing titer of palivizumab. Applicants have also amended claims 85 and 87 (and claims dependent therefrom) to recite a method of preventing a RSV infection in a human subject by administering a prophylactically effective amount of a ***palivizumab sustained release formulation*** or a palivizumab pharmaceutical composition. Further, Applicants have amended claims 180 and 181 (and claims dependent therefrom) to recite a method of preventing or treating a RSV infection in a human subject by administering an amount of a palivizumab composition that results in a concentration of at least 20 ng per mg of lung protein at least 20 days after administration.

None of the cited references cited in the Office Action, alone or in combination, teach or suggest the claimed invention. Johnson describes the ***intramuscular*** or ***intravenous*** administration of MEDI-493 to cotton rats and the prophylactic effect achieved. Johnson does ***not*** disclose a sustained release formulation or a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab. There is no teaching or suggestion in Johnson to produce a sustained formulation or a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab, much less a method of preventing or treating a RSV infection in a ***human subject*** by administering to the human subject a ***sustained release formulation*** comprising palivizumab, or administering to the ***lungs*** of the human subject a ***pharmaceutical composition adapted for pulmonary delivery***. Rather, the focus of Johnson is to assess the ability of MEDI-493 to neutralize RSV in ***cotton rats***.

Moreover, Johnson does not provide a motivation to produce a sustained release formulation or a pharmaceutical composition adapted for pulmonary delivery. At best, Johnson points out that MEDI-493, based on its potency and safety in cotton rats, ***potentially*** has utility in the prevention of a RSV infection in infants and states that clinical trials have been initiated to investigate its prophylactic utility. Thus, Johnson does not teach or suggest the compositions or methods of presently pending claims 73, 74, 85-94 and 99-110.

Further, Johnson does not teach or suggest a method of preventing or treating a RSV infection in a ***human subject*** by administering to the ***lungs*** of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab or an antigen-binding fragment thereof, said effective amount resulting in a ***concentration of at least 20 ng per mg of lung protein at least 20 days after administration*** of the first dose and before the administration of a subsequent dose. There is no teaching or suggestion in Johnson to prevent or treat a RSV infection in humans, much less a method of preventing or treating a RSV infection by administering to the lungs of a human subject a palivizumab composition. Moreover, there is no teaching or suggestion in Johnson regarding a method of preventing or treating a RSV infection by administering an amount of palivizumab effective to achieve a concentration of at least 20 ng per mg of lung protein at least 20 days after administration. Accordingly, Johnson does not render presently pending claims 180, 181, 186, 187 and 189-190 obvious.

The deficiencies in Johnson are not cured by the secondary references. The Package Insert sets forth a description of Synagis® (palivizumab) and the intramuscular administration of Synagis® to prevent a RSV infection in pediatric patients. The Package Insert does not teach or suggest sustained release formulations comprising palivizumab, much less methods of preventing or treating a RSV infection by administering such formulations to a human subject. Moreover, the Package Insert does not teach or suggest pharmaceutical compositions adapted for pulmonary delivery comprising palivizumab, much less methods of preventing or treating a RSV infection by administering such formulations to the lungs of a human subject. Accordingly, the Package Insert, alone or in combination, does not render presently pending claims 73, 74, 85-94 and 99-110 obvious.

Further, the Package Insert does not teach or suggest a method of preventing or treating a RSV infection in a ***human subject*** by administering to the ***lungs*** of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab or an antigen-binding fragment thereof, said effective amount resulting in a ***concentration of at least 20 ng per mg of lung protein at least 20 days after administration*** of the first dose and before the administration of a subsequent dose.

Accordingly, the Package Insert, alone or in combination, does not render presently pending claims 180, 181, 186, 187 and 189-190 obvious.

Lam does not cure the deficiencies in Johnson or the Package Insert. Lam merely describes a controlled release formulation for an anti-VEGF Fab fragment. Lam does ***not*** describe or suggest a formulation for the sustained release of a humanized antibody, much less a humanized RSV monoclonal antibody such as palivizumab. As previously discussed in Paper No. 14, a ***humanized RSV monoclonal antibody*** such as palivizumab is ***structurally and functionally different*** from a ***Fab fragment*** of a ***VEGF*** monoclonal antibody. Lam only describes manipulation of various parameters with respect to a specific Fab fragment of a VEGF humanized monoclonal antibody. Indeed, many of the parameters that Lam manipulated to achieve microencapsulation of the Fab fragment of the VEGF humanized monoclonal antibody for controlled release were dependent on factors such as the stability and the size of the Fab fragment, and would not be expected by one of skill in the art to be applicable to the entire VEGF humanized monoclonal antibody, much less a humanized monoclonal immunospecific for a RSV antigen such as palivizumab. Applicants submit that other humanized monoclonal antibodies would have a different structure, function or pharmacokinetic profile than the VEGF Fab fragment described in Lam. Thus, one of skill in the art would not have been motivated to combine the teachings of Lam with Johnson or the Package Insert to produce a sustained release formulation comprising palivizumab. Moreover, based upon Lam, one of skill in the art would ***not*** have a reasonable expectation that the controlled release formulation described in Lam could be successfully applied to other humanized antibodies such as palivizumab. Accordingly, Lam, alone or in combination, does not render obvious presently pending claims 73, 85 86, 89-92, 99, 100, and 103-106, directed to a sustained release formulation comprising palivizumab or methods of preventing or treating a RSV infection in a human subject by administering said formulation.

Moreover, Lam does not teach or suggest a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab, much less methods of preventing or treating a RSV infection by administering to the lungs of a human subject such a composition. As discussed above, Lam merely describes a controlled release formulation for an anti-VEGF Fab fragment. Accordingly, Lam, alone or in combination, does not render obvious presently pending claims 74, 87, 88, 93, 94, 101, 102 and 107-110, directed to a pharmaceutical composition adapted for pulmonary delivery comprising palivizumab or methods of preventing or treating a RSV infection in a human subject by administering to the lungs of the human subject the composition.

Further, Lam does not teach or suggest a method of preventing or treating a RSV infection in a ***human subject*** by administering to the ***lungs*** of the subject a first dose of a prophylactically or therapeutically effective amount of a composition comprising palivizumab or an antigen-binding fragment thereof, said effective amount resulting in a ***concentration of at least 20 ng per mg of lung protein at least 20 days after administration*** of the first dose and before the administration of a subsequent dose. Lam merely describes a controlled release formulation of a Fab fragment of a VEGF humanized monoclonal antibody. Accordingly, Lam, alone or in combination, does not render presently pending claims 180, 181, 186, 187 and 189-190 obvious.

In view of the foregoing, Applicants respectfully assert that the rejections under 35 U.S.C. § 103(a) cannot stand and should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing remarks. Applicants believe that all of the present claims meet all of the requirements for patentability. Withdrawal of all rejections is requested.

If any issues remain, the Examiner is requested to telephone the undersigned at (212) 790-9090.

Respectfully submitted,

Date: May 5, 2003

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